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EXAMINER
YOUNG, JOSEPHINE

ART UNIT	PAPER NUMBER
1623	8

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Please find below and/or attached an Office communication concerning this application or proceeding.

Offic Action Summary	Application No. 09/868,348	Applicant(s) POTTER ET AL.	
	Examiner Josephine Young	Art Unit 1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence addr ss --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 December 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,8,15 and 19-31* is/are pending in the application.

4a) Of the above claim(s) *15 and 29-31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,8 and 19-28* is/are rejected.

7)☒ Claim(s) *8* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I in Paper No. 7, transmitted via facsimile on December 2, 2002, is acknowledged. The traversal is on the ground(s) that Applicant believes that Groups I, II and III do exhibit unity of invention under PCT Rule 13.2 because there is a technical relationship among the claimed inventions. This is not found persuasive. While it is recognized that Groups I, II and III have a common technical feature involving compounds that modulate the sustained rise in Ca^{+2} entry via a cADPR-mediated pathway, the requirement under PCT Rule 13.2 is that there be a common **special** technical feature, wherein the special technical feature is one that is a contribution over the prior art. Applicant's opinion with regard to the novelty and inventiveness of the present application is appreciated. However, International Publication WO 98/43992 to GALIONE (previously cited) teaches several compounds that are cADPR-antagonists. Therefore, the technical feature linking Groups I, II and III cannot be compounds that modulate the sustained rise in Ca^{+2} entry via a cADPR-mediated pathway.

The special technical feature of Group I is considered to be methods for modulating T cell activation and for treating related diseases.

The special technical feature of Group II is considered to be methods for identifying substances capable of modulating sustained rise in Ca^{+2} entry via a cADPR-mediated pathway.

The special technical feature of Group III is considered to be compounds identified using the assay of Group II.

The lack of unity is maintained for the reasons of record. The requirement is still deemed proper and is therefore made FINAL.

Accordingly, claims 15 and 29-31 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Drawings

The drawings are objected to because the y-axis of Figure 2a-e is labeled in Greek. A proposed drawing correction or corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

Specification

The disclosure is objected to because of the following informalities: In Example 3, page 10, lines 10-11, 14-15 and 16, inositol 1,4,6-trisphosphorothioate is referred to as Ins(1,4,6)PS_3. However, in Figure 3, the compound is referred to as Ins(1,4,6)P_3S or I(1,4,6)P_3S.

Appropriate correction is required.

Claim Objections

Claim 8 is objected to because of the following informalities: Claim 8 depends from cancelled claim 10. For the purposes of this Office Action, it was assumed that claim 8 comprises all the limitations of the cancelled parent claim(s). Appropriate correction is required.

Claim 21 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim, claim 1. The modulation of T cell activation of claim 1 is considered to be the same as the modulation of an immune response of claim 21. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Undue experimentation is a conclusion reached by weighing the noted factual considerations set forth below in In re Wands USPQ2d 14000. A conclusion of lack of enablement means that, based on the evidence regarding a fair evaluation of an appropriate combination of the factors below, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention.

These factors include

(1) quantity of experimentation necessary,

(2) the amount of guidance presented,

(3) the presence or absence of working examples,

(4) the nature of the invention,

(5) the state of the prior art,

(6) the predictability of the art and

(7) the breath of the claims.

Claims 1-5, 8 and 20-28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for decreasing T cell activation and for treating rheumatoid arthritis using 7-deaza-8-Br-cADPR, does not reasonably provide enablement for decreasing T cell activation and for treating autoimmune diseases using any compound in general. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

With regard to factors (1) and (2) cited above, undue experimentation is required to determine which compounds would be useful in antagonizing a sustained cADPR-mediated rise in intracellular Ca^{+2} levels in a T-cell to stimulate the T cell receptor/CD_3 complex to use for modulating T cell activation and diseases related to T cell activation such as immune disorders for which the instant invention is applicable. There has not been provided adequate guidance in the written description for accomplishing such, as only 7-deaza-8-Br-cADPR was assessed, out of the numerous compounds that antagonize a sustained cADPR-mediated rise in intracellular Ca^{+2} levels known in the art, let alone the infinite number of compounds that have not yet been screened for such activity.

With regard to factors (4), (5) and (6), it is noted that there is a great deal of unpredictability in the art. For example, various compounds are known to antagonize cADPR, however, there are remarkable differences in the antagonistic effects of such compounds based on different cell types. Further, there is no discernable pattern as to which compound will be effective in which cell type. See for example GUSE et al., Journal of Immunology, **1995**, *155*,

3353-3359 (U), and in particular page 3357, last paragraph. "[T]he cADPR-responsive systems in both sea urchin eggs and T cells are somewhat different in terms of sensitivity to cADPR and different antagonists" (page 3358, right column, lines 12-14). The art at the time the invention was made fails to establish predictability with regard to the properties of the compounds needed to perform the methods as instantly claimed.

With regard to factors (3) and (7), it is noted that while there is one working example using 7-deaza-8-Br-cADPR, it is not seen as sufficient to support the breath of the claims. It is noted that Law requires that the disclosure of an application shall inform those skilled in the art how to use applicant's alleged discovery, not how to find out how to use it for themselves. See In re Gardner et al. 166 USPQ 138 (CCPA 1970).

Claims 8 and 23-27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for decreasing T cell activation and for treating rheumatoid arthritis, does not reasonably provide enablement for treating any immune disorder other than rheumatoid arthritis, such as graft rejection or an autoimmune disorder, for example thyroiditis, insulitis, multiple sclerosis, iridocyclitis, uveitis, orchitis, hepatitis, Addison's disease, myasthenia gravis and lupus erythematosus. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

With regard to factors (1) and (2) cited above, undue experimentation is required to determine which immune disorder would be effected by decreasing T cell activation using the recited compounds for which the instant invention is applicable. There has not been provided

adequate guidance in the written description for accomplishing and determining such, as only one disorder, namely rheumatoid arthritis, was assessed via antigen-induced arthritis (AIA) in mice, out of the numerous known disorders that effect and are effected by the immune system.

With regard to factors (4), (5) and (6), it is noted that there is a great deal of unpredictability in the art. For example, while certain agents and compositions are known to treat certain forms of immune disorders, no effective agent or composition has been found for the treatment of all immune disorders. Therefore, the art at the time the invention was made fails to establish predictability with regard to the properties of the compounds needed to perform the scope of the methods as instantly claimed.

With regard to factors (3) and (7), it is noted that while there are some working examples of the treatment of rheumatoid arthritis related to antigen-induced arthritis (AIA) in mice, it is not seen as sufficient to support the breath of the claims. It is noted that Law requires that the disclosure of an application shall inform those skilled in the art how to use applicant's alleged discovery, not how to find out how to use it for themselves. See In re Gardner et al. 166 USPQ 138 (CCPA 1970).

Claims 1-5, 8, 19-22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for decreasing T cell activation and for treating rheumatoid arthritis in vivo, does not reasonably provide enablement for modulating T cell activation ex vivo. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

With regard to factors (1) and (2) cited above, undue experimentation is required to determine which compounds would be effective in ex vivo modulation of T cell activation for which the instant invention is applicable. There has not been provided adequate guidance in the written description for accomplishing and determining such, as no ex vivo assays were specifically disclosed or assessed.

With regard to factors (4), (5) and (6), it is noted that there is a great deal of unpredictability in the art. For example, while certain agents and compositions are known to treat certain forms of immune disorders in vivo, such compounds may not necessarily be effective ex vivo. Therefore, the art at the time the invention was made fails to establish predictability with regard to the properties of the compounds needed to perform the scope of the methods as instantly claimed.

With regard to factors (3) and (7), it is noted that there are no working examples. It is noted that Law requires that the disclosure of an application shall inform those skilled in the art how to use applicant's alleged discovery, not how to find out how to use it for themselves. See In re Gardner et al. 166 USPQ 138 (CCPA 1970).

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-5, 8 and 19-28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "modulating" and "modulated in claims 1-5, 8 and 19-28 renders the claims in which it appears indefinite. While it is clear as how T cell activation can be decreased by antagonizing a sustained cADPR-mediated rise in intracellular Ca+2 levels, it is unclear as to how T cell activation can be modulated in a way other way.

The term "sustained" in claims 1 and 23 is a relative term that renders the claims in which it appears indefinite. The term "sustained" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is unclear as to how long of a rise in intracellular Ca^{+2} levels constitutes a sustained rise.

The term "cADPR analogue" in claims 3 and 25 renders the claims in which it appears indefinite. In the absence of the specific modification to cADPR or distinct language to describe the structural modifications or the chemical names of the cADPR analogue of this invention, the identity of said cADPR analogue would be difficult to describe and the metes and bounds of said cADPR analogue Applicant regards as the invention cannot be sufficiently determined because they have not been particularly pointed out or distinctly articulated in the claims.

The compound of formula (2) in claims 5 and 27 renders the claims in which it appears indefinite. There is a positive charge on nitrogen; however, it is unclear as to what the counter ion would be to balance the charge of the compound.

The term "bio-isostere" in claims 5, 20 and 27 renders the claims in which it appears indefinite. In the absence of the specific modification to the compounds or distinct language to describe the structural modifications or the chemical names of the modified compounds of this invention, the identity of said bio-isostere would be difficult to describe and the metes and

bounds of said bio-isostere Applicant regards as the invention cannot be sufficiently determined because they have not been particularly pointed out or distinctly articulated in the claims.

The phrase "Z is independently selected from the group consisting of ... a bio-isostere and a pharmaceutically acceptable salt thereof" in claims 5 and 27 renders the claims in which it appears indefinite. It is unclear as to how Z can be a bio-isostere or salt.

Similarly, the phrase "R_3 is selected from the group consisting of ... a bio-isostere and a pharmaceutically acceptable salt thereof" in claim 20 renders the claim in which it appears indefinite. It is unclear as to how R_3 can be a bio-isostere or salt.

The compound of formula (3) and (4) in claim 20 renders the claims in which it appears indefinite. It is unclear as to what R and R^6 are referring. It is also unclear as to if R_1 and R_2 in formulas (3) and (4), are the same as R^1 and R^2, with respect to NHR^1R^2 in the definition of Z and X. Further, it is unclear as to how Z and X can be NHR^1R^2.

Claim 22 recites the limitation "wherein T cells are removed from a mammalian patient, treated with the compound, and then returned to the patient". There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-5, 8 and 19-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over SETHI et al., Journal of Biological Chemistry, **June 27, 1997**, *272* (26), 16358-16363 (V) in view of GUSE (U) and GUSE (AC, PTO-1449, paper no. 5).

Applicant claims methods for decreasing T cell activation, in vivo and ex vivo, using a compound that antagonizes a sustained cADPR-mediated rise in intracellular Ca^{+2} levels in response to stimulation of the T cell receptor/CD3 complex of the T cell, for example via a ryanodine receptor/calcium channel. Such compounds include cADPR analogues, for example compounds of the formula (2), (3) or (4), and in particular, 7-deaza-8-Br-cADPR and 8-Br-cADPR. Further Applicant claims methods of treating an immune disorder, such as rheumatoid arthritis, using such compound by decreasing T cell activation as a result of antagonizing a sustained cADPR-mediated rise in intracellular Ca^{+2} levels in response to stimulation of the T cell receptor/CD3 complex of the T cell.

SETHI teaches that 7-deaza-8-Br-cADPR is a hydrolysis resistant cADPR receptor antagonist that is membrane permeable. See Abstract. Further, in the Abstract, SETHI teaches that cADPR is considered an endogenous regulator of ryanodine-sensitive Ca^{+2} release channels. On page 16361, left column, lines 5-9, SETHI discloses that such compounds would be useful as

antagonists in intact cells/tissues, "such as Jurkat T cells ... that express high hydrolase activities but may have a functional cADPR-mediated Ca^{+2}-signaling pathway."

SETHI does not explicitly state that the result of antagonizing the cADPR receptor in T cells would lead to a decrease in T cell activation. Further, SETHI does not specifically state that such antagonists could be used to treat an immune disorder. Finally, SETHI does not teach that the modulation of T cell activation can be accomplished ex vivo.

GUSE (U) teaches that cADPR is present endogenously in Jurkat and HPB.ALL T cells such that cAPDR dose-dependently and specifically released Ca^{+2} from an intracellular Ca^{+2} pool of Jurkat and HPB.ALL T cells. See last paragraph on page 3359. Further, in that same paragraph, GUSE (U) teaches that TCR/CD3 (i.e., T cell receptor/CD3 complex) triggering is linked to formation of cADPR.

GUSE (AC) teaches that immunosuppressive drugs can be developed based on the mechanism of activation of calcium channels in T cells. See Conclusions on page 440. Further, GUSE (AC) teaches on page 425, right column, penultimate paragraph, that FK506, a known immunosuppressant, may act by altering calcium dependent activation via binding to cADPR.

It would have been obvious to one of ordinary skill in the art to use the cADPR receptor antagonists of SETHI to decrease T cell activation, as GUSE (U) and GUSE (AC) teaches that modulation of cADPR would have implications on T cell activation. A skilled artisan would have been motivated and have had a reasonable expectation of success, as SETHI teaches that such antagonists would be useful in T cells. Further, it would have been obvious to one of ordinary skill in the art to use such compounds for the treatment of an immune disorder as GUSE (AC) teaches that a known immunosuppressant potentially is effective via this method of

inactivation. Finally, if Applicant deems that the claims directed to ex vivo methods are enabled by the specification (i.e. that there is predictability in the art), then the ex vivo modulation of T cell activation is considered a choice in experimental design, and within the purview of the prior art.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Josephine Young whose telephone number is (703) 605-1201. The examiner can normally be reached on Monday through Friday, 9:00 a.m. to 6:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached at (703) 308-4624. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3014 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

JY
February 10, 2003

JAMES O. WILSON
SUPERVISORY PATENT EXAMINER
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